

Applicants : Philip O. Livingston and Friedhelm Helling  
U.S. Serial No.: 08/475,784  
Filed : June 7, 1995  
Page 5

matter. Accordingly, claims 53, 55-57 and 59-77 will be pending upon entry of this amendment.

#### Specification

The Examiner stated that the prior objection to the disclosure is maintained for the reasons as set forth in the last Office Action mailed June 10, 1996 (see Paper No. 9). The Examiner stated that applicants said they they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. The Examiner stated that until applicants submit a proper Figure said objection is maintained.

In response, without conceding the correctness of the Examiner's position but to expedite the prosecution of the subject application, applicants will submit a new figure 6B upon the indication of allowable subject matter.

#### Double Patenting

The Examiner stated that claims 53-72 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims 53-71 of copending Application No. 08/477,097.

The Examiner stated that applicants assert that the added new claims in the copending application obviate the obvious-type double patenting. The Examiner stated that applicants arguments are not persuasive since the claims of the instant application encompass conjugating the ceramide portion of GM2 as recited in copending application 08/477,097.

The Examiner stated that claim 43-72 are provisionally rejected under the judicially doctrine of obviousness-type double patenting

Applicants : Philip O. Livingston and Friedhelm Helling  
U.S. Serial No.: 08/475,784  
Filed : June 7, 1995  
Page 6

as being unpatentable over claims 44 and 46-56 of copending Application Nos. 08/477,147 and 08/481,809.

The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the prior Office Actions.

The Examiner stated that applicants argue that they will add new claims in 08/477,147 and 08/481,089 and that they believe the added new claims in the applications will obviate the obvious type double patenting. The Examiner stated that applicants arguments are noted, however, until said claims are added said rejection is maintained for the reasons of record. The Examiner stated that furthermore the Examiner suggests that applicants provide a copy of the claims in the copending application in the next Office Action.

In response, applicants respectfully traverse the above rejection. Nevertheless, without conceding the correctness of the Examiner's position but to expedite the prosecution of the subject application, applicants have hereinabove amended the claims. In addition, applicants have amended the claims in the copending applications. Applicants contend that these amendments and remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

Rejection Under 35 USC §112 First Paragraph

The Examiner rejected claims 53-57 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed June 10, 1996 (see Paper No. 9).

Applicants : Philip O. Livingston and Friedhelm Helling  
U.S. Serial No.: 08/475,784  
Filed : June 7, 1995  
Page 7

The Examiner stated that applicants' amendment is sufficient to obviate the objection to the specification for: 1) the use of other gangliosides or chemically modified gangliosides; and 2) use of the claimed product as a vaccine. The Examiner stated that however, the specification provides insufficient guidance of how to use derivatives of KLH as recited. The Examiner stated that applicants assert that by routine experimentation one skilled in the art is enabled to make derivatives of KLH (see Applicants arguments on Paper NO. 12; page 4.) The Examiner stated that applicants assert that the derivatives of KLH can be tested using the KLH disclosed in the specification. The Examiner stated that applicants arguments are not persuasive.

The Examiner stated that Protein chemistry is probably one of the most unpredictable areas of biotechnology, for example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). The Examiner stated that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or aspartic did not affect biological activity while replacement with serine of glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). The Examiner stated that Rudinger et al, teaches "particular amino acids and sequences from case to case by painstakingly experimental study" (see page 6). The Examiner stated that Salgaller et al teach modification (i.e. deletions) of the amino acid structure of peptide can alter the activity of the protein. The Examiner stated that Fox et al teach method for determining fragments which have antigenic activity is unpredictable. The Examiner stated that these references demonstrate that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological

Applicants : Philip O. Livingston and Friedhelm Helling  
U.S. Serial No.: 08/475,784  
Filed : June 7, 1995  
Page 8

activity of a protein. The Examiner stated that in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad or derivatives and fragments encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

The Examiner stated that contrary to applicants arguments it is reasonable to conclude an undue burden is required to screen for positions within the sequence where amino acid modification (i.e. addition, deletions, or modifications) can be made with a reasonable expectation of success in obtaining similar activity/utility are limited and the result of such modifications is unpredictable as exemplified by the teachings of Lazar et al., Burgess et al., Rudinger et al., and Salgaller et al. The Examiner stated that these references demonstrate that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein.

The Examiner stated that the specification does not support the broad scope of the claims which encompass a multitude of analogs or equivalents because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions which can be predictably modified; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

The Examiner stated that thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with

Applicants : Philip O. Livingston and Friedhelm Helling  
U.S. Serial No.: 08/475,784  
Filed : June 7, 1995  
Page 9

the scope of the claims broadly including any number of deletions, additions, and/or substitutions of any size. The Examiner stated that the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The Examiner stated that without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

The Examiner stated that applicants cite to page 12, lines 4-13 of the specification for support of using derivatives of KLH. The Examiner stated that said disclosure is not commensurate in scope with the claimed invention. The Examiner stated that said cite makes reference only to linking KLH to an "immunological adjuvant" **and not** amino acid modifications (i.e. deletions, substitutions) of KLH. The Examiner stated as set forth above the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The Examiner stated that for the reason set forth above and in the last Office Action said rejection is maintained.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the claimed invention is enabled. Applicants maintain that the specification provides sufficient teachings which enable one skilled in the art to generate such derivatives. See Specification page 12, lines 4-13. Applicants also described some routine experiments on page 4, second paragraph of the January 6, 1997 Supplemental Communication in Response to June 10, 1996 Office Action to generate said derivatives. Regarding the Examiner's specific comments about the variation of one or a few amino acids which may change the property of a protein, the disclosed specification has provided specific

Applicants : Philip O. Livingston and Friedhelm Helling  
U.S. Serial No.: 08/475,784  
Filed : June 7, 1995  
Page 10

embodiments of Keyhole Limpet Hemocyanin being used as the immunogenic protein. The derivatives generated may easily be tested using the specific Keyhole Limpet Hemocyanin disclosed in the specification for comparison. Accordingly, there is no undue experimentation and applicants maintain that the derivatives of Keyhole Limpet Hemocyanin are fully enabled by the specification as filed.

Applicants contend that these remarks and amendments obviate the Examiner's above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

Rejection Under 35 U.S.C. 112, First Paragraph

The Examiner rejected claims 53-72 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner stated that the original specification does not provide an adequate written description of conjugating a ceramide portion to the ganglioside (i.e. GM2, GM3, GD2, GD3 lactone, O-acetyl GD3, GT3) as claimed. The Examiner stated that the specification as originally filed only provides support of conjugating GD3 by the ceramide portion (see page 32. The Examiner acknowledges applicants remarks for support of claimed subject matter. The Examiner stated that however, applicants remarks are not directed to conjugating a ceramide portion to the ganglioside as claimed. The Examiner invites applicants to point by page and line number for conjugating the ganglioside by the ceramide portion as newly submitted.

Applicants : Philip O. Livingston and Friedhelm Helling  
U.S. Serial No.: 08/475,784  
Filed : June 7, 1995  
Page 11

In response, applicants respectfully traverse the above rejection. Applicants contend that the specification conveys to one skilled in the art that applicants had possession of the claimed subject matter at the time of filing. Applicants respectfully direct the Examiner's attention to page 32, lines 13-18 of the specification. Applicants maintain that this teaches a general method for the conjugation of gangliosides through the ceramide portion. Applicants contend that one skilled in the art would understand that this approach would be applicable to other gangliosides, not just GD3. Applicants contend that conjugations of other gangliosides were envisioned at the time of filing, as evidenced by the disclosure on page 12, lines 22-26. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claim 53-67, and 69-72 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663) and Ritter et al. (1990) and further in view of Kensil et al and Marciani et al. for the reasons set forth in the Office Action mailed June 13, 1996 (see Paper No. 8; items 10 and 11).

The Examiner stated that applicants appear to argue the rejection should be withdrawn since the prior art does not suggest or provide an expectation of conjugating the ganglioside to the KLH through the ceramide portion of the ganglioside. The Examiner stated that applicants arguments are not persuasive.

The Examiner stated that Ritter et al. (1990) teaches conjugating GM2 to KLH gives specific antibodies to GM2 (see page 406). The

Applicants : Philip O. Livingston and Friedhelm Helling  
U.S. Serial No.: 08/475,784  
Filed : June 7, 1995  
Page 12

Examiner stated that additionally Ritter et al. 1990 teaches the gangliosides differ most obviously from each other in their carbohydrate moieties (see page 401). The Examiner stated that accordingly, it would have been expected the KLH is bound to the ceramide portion, particularly since the antibodies of the ganglioside bind to the hydrophilic portion (i.e. carbohydrate portion) as exemplified by Ritter et al. 1991 who sets forth that alteration of the carbohydrate moiety affect binding of antibody.

The Examiner stated that applicants assert that the prior art does not teach of composition comprising a carbohydrate derivable from the bark from the tree as recited. The Examiner stated that applicants arguments are not persuasive in view of the teaches of Kensil et al who sets forth using QS-21 which was purified from Quilaja saponaria Molina (see abstract).

The Examiner stated that applicants assert the prior art does not teach of the ganglioside conjugate. The Examiner stated that applicants argument is not persuasive for the reasons set forth above.

In response, applicants respectfully traverse the Examiner's above rejections. Applicants contend that the cited references do not teach, suggest or disclose applicants claimed invention. Nevertheless, without conceding the correctness of the Examiner's position but to expedite the prosecution of the subject application, applicants have hereinabove added new claims to further specify the conjugation. Applicants contend that none of the cited references alone or in combination teach the claim that will be pending upon entry of this amendment. Specifically, the new claims now specify that the conjugation of the ganglioside is through: (a) a ceramide-derived carbon, (b) carbon derived from a cleavage of a double bond in the ceramide portion of the



Applicants : Philip O. Livingston and Friedhelm Helling  
U.S. Serial No.: 08/475,784  
Filed : June 7, 1995  
Page 13

ganglioside, (c) carbon derived from a ceramide double bond to Keyhole Limpet Hemocyanin or a derivative thereof, (d) ceramide double bond of the ganglioside and a reactive amine group of Keyhole Limpet Hemocyanin or a derivative thereof, or (e) ceramide double bond of the ganglioside and an aminolysl group of Keyhole Limpet Hemocyanin or a derivative thereof. Applicants contend that these remarks and amendments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

**Rejection Under 35 U.S.C. 103(a)**

The Examiner rejected claim 68 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Livingston et al., Kensil et al and Marciani et al. as applied to claims 53-67, and 69-72 above and further in view of Irie et al.

The Examiner stated that Livingston et al. (Cancer Research), Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Livingston et al., Kensil et al nor Marciani et al. Do not teach of administering the vaccine for treating cancer of epithelial origin.

The Examiner stated that Irie et al. Teachings are set forth in the Office Action mailed June 13, 1996 (see Paper No. 8; item 12).

The Examiner stated that one of ordinary skill in the art to administer the vaccine to patient afflicted with or susceptible to cancer of epithelial origin in view of the reasons set forth in Office Action mailed June 13, 1996 (see Paper No. 8; item 12).

Applicants : Philip O. Livingston and Friedhelm Helling  
U.S. Serial No.: 08/475,784  
Filed : June 7, 1995  
Page 14

The Examiner stated that applicants appear to argue the rejection should be withdrawn since the prior art does not suggest or provide an expectation of making the claimed invention as applied to claims above. For reasons set forth above applicants arguments are not persuasive. The Examiner stated that the prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The Examiner stated that Ritter et al. (Exhibit 13) discloses of a GD3 amide derivative and that said derivatives had the highest antibody response (see page 38).

In response, applicants respectfully traverse the Examiner's above rejections. Applicants contend that the cited references do not teach, suggest or disclose applicants claimed invention. Nevertheless, without conceding the correctness of the Examiner's position but to expedite the prosecution of the subject application, applicants have hereinabove added new claims which further specify the conjugation. Applicants contend that none of the cited references alone or in combination teach the claim that will be pending upon entry of this amendment. Specifically, the claim now specifies that the conjugation of the ganglioside is through (a) a ceramide-derived carbon, (b) carbon derived from a cleavage of a double bond in the ceramide portion of the ganglioside, (c) carbon derived from a ceramide double bond to Keyhole Limpet Hemocyanin or a derivative thereof, (d) ceramide double bond of the ganglioside and a reactive amine group of Keyhole Limpet Hemocyanin or a derivative thereof, or (e) ceramide double bond of the ganglioside and an aminolysl group of Keyhole Limpet Hemocyanin or a derivative thereof. Applicants contend that these remarks and amendments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

Applicants : Philip O. Livingston and Friedhelm Helling  
U.S. Serial No.: 08/475,784  
Filed : June 7, 1995  
Page 15

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection and earnestly solicit allowance of the claims now pending in the subject application.

No fee is deemed necessary in connection with the filing of this Amendment. However, if additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Albert Wai-Kit Chan

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.	
<u>Albert Wai-Kit Chan</u> Albert Wai-Kit Chan Reg. No. 36,479	<u>6/30/99</u> Date

John P. White  
Registration No. 28,678  
Albert Wai-Kit Chan  
Registration No. 36,479  
Attorneys for Applicants  
Cooper & Dunham LLP  
1185 Avenue of the Americas  
New York, New York 10036  
(212) 278-0400